Title: Homocysteine, rather than age of onset, is a better predictor for cognitive function in older adults with bipolar disorder

Authors:

Pao-Huan Chen [1,2], Hsing-Cheng Liu [2,3], Mong-Liang Lu [2,4], Chun-Hsin Chen [2,4], Ching-Jui Chang [5], Wei-Che Chiu [5], I-Wen Sun [6], Shen-Ing Liu [6], Shang-Ying Tsai [1,2], Chih-Chiang Chiu [2,3], Robert Stewart [7,8]

[1] Department of Psychiatry, Taipei Medical University Hospital, Taipei, Taiwan

No. 252, Wu-Hsing Street, Taipei, 110, Taiwan

[2] Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

No. 250, Wu-Hsing Street, Taipei, 110, Taiwan

[3] Department of Psychiatry, Taipei City Psychiatric Center, Taipei City Hospital, Taipei, Taiwan

No. 309, Songde Road, Taipei 110, Taiwan

[4] Department of Psychiatry, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan

No. 111, Sec. 3, Hsin-Long Rd, Taipei 116, Taiwan

[5] Department of Psychiatry, Cathay General Hospital, Taipei, Taiwan

No. 280, Sec.4, Renai Road, Taipei 106, Taiwan

[6] Department of Psychiatry, Mackay Memorial Hospital Taipei, Taiwan

No. 92, Sec. 2, Zhongshan N. Road, Taipei 110, Taiwan

[7] King's College London, Institute of Psychiatry, Psychology and Neuroscience,

De Crespigny Park, London SE5 8AF, United Kingdom

[8] South London and Maudsley NHS Foundation Trust

Denmark Hill, London SE5 8AF, United Kingdom

Address correspondence to:

Dr. Chih-Chiang Chiu

Department of Psychiatry, Taipei City Psychiatric Center, Taipei City Hospital

#309, Song-De Road, Taipei 110, Taiwan

E-mail: eric.ccchiu@gmail.com

Tel: +886-2-27263141 ext. 1346

Fax: +886-2-27285059

Running title: Homocysteine and cognition in older bipolar disorder

Word count of the body text: 2881

Acknowledgments: We thank Ms. Su-Chen Chang and Ms. Chia-Chen Hsu for their excellent work on participant recruitment, laboratory work, and data management.

Funding: This work is supported by Taipei City Hospital and the National Science Council (MOST 105-2314-B-532-003-MY3) of Taiwan; and RS is part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre, Dementia Biomedical Research Unit at South London and Maudsley NHS Foundation Trust, and King's College London of UK.

Abstract

Objectives: The association between older-age bipolar disorder and cognitive impairments may be mediated by vascular burden. The aim of the study was to examine the difference of cognitive function between older people with late-onset bipolar disorder (LOBD) and early-onset bipolar disorder (EOBD) by considering rigorous vascular risk burden evaluation, comprehensive cognitive tests, and relevant biochemistry data.

Methods: We recruited 95 outpatients aged over 55 with a DSM-IV-TR diagnosis of bipolar I disorder. Fifty had LOBD, defined by age of onset after 40. Cognitive function was evaluated through a battery of tests assessing verbal memory, attention/speed, visuospatial function, verbal fluency, and cognitive flexibility. Vascular risk assessments included individual disorders, 10-year Framingham cardiovascular risk scores, and serum levels of homocysteine, vitamin B12, folate, and triiodothyronine.

Results: No differences were observed between LOBD and EOBD on any cognitive test after adjusting for potential confounders. In addition to age and educational years, multiple linear regression analyses indicated significantly negative associations between serum homocysteine levels and cognitive performances in attention, psychomotor speed, verbal memory, and executive function.

Conclusions: Among older people with bipolar disorder, LOBD is not associated with more cognitive dysfunction in this study. However, higher serum homocysteine levels were significantly associated with worse cognitive performance in this particular group. Clinicians therefore have to pay attention to the cognitive function in older bipolar patients with higher levels of homocysteine.

Keywords: age of onset; Framingham risk score; homocysteine; neurocognitive performance; older-age bipolar disorder

Key points

- About one third of older patients with bipolar disorder have cognitive impairment.
- This study found that higher serum levels of homocysteine were significantly associated with worse cognitive performance in attention, psychomotor speed, verbal memory, and executive function among older patients with bipolar disorder.
- Late-onset bipolar disorder was not associated with more cognitive dysfunction in this study. This may be due to similar cardiovascular risk between late- and early-onset bipolar disorder.

1. Introduction

Bipolar disorder (BD) is a severe mental disorder characterized by recurrence of multiple manic or depressive episodes. In addition to the mood burden, patients with BD also suffer from several unfavorable outcomes, including high levels of medical comorbidities and cognitive deficits.[1-3] Studies have repeatedly shown that at least one third of older patients with euthymic BD have cognitive impairments.[4-6] A recent meta-analysis concluded that history of BD was associated with an approximately two-fold increased risk of dementia.[7] However, different risk factors of cognitive impairment have been shown for this specific group, including aging effects,[6,8] unhealthy lifestyle,[9] reduced cognitive reserve,[10,11] and high burden of vascular comorbiditie.[12,13] The underlying causal pathways are poorly understood.

In the literature, late-onset bipolar disorder (LOBD) is considered to be different from early-onset BD (EOBD) with respect to the pathophysiology and clinical presentation.[3] Compared to patients with EOBD, those with LOBD are found to have more cerebrovascular diseases,[14] and more severe cognitive impairment.[15,16] However, evidence from other researches does not show more cognitive deficits in LOBD,[17,18] which was supported by that cognitive impairment in older patients with BD may be related to the length of BD illness and number of hospitalizations.[13,19] Neuroimaging studies also have indicated a negative correlation between gray matter volume and

length of BD illness in older patients with BD.[20] Altogether, these findings suggest that age of onset may not be a reliable predictor of cognitive dysfunction in older patients with BD.

Higher vascular burden has been shown to be the robust risk factor for cognitive deficits in general population[21,22] as well as in older patients with BD.[13] Since LOBD has been found to be more related to vascular diseases,[18,23] the association between LOBD and cognitive impairments may be mediated by the vascular burden. However, previous studies did not find that LOBD patients with more severe cognitive impairment have a significantly higher cerebrovascular disease index.[15] One possible explanation for the negative findings may be due to the measures used to assess the vascular risk factors. For example, the Framingham cardiovascular risk score model has been demonstrated as a valid tool to predict cognitive deficits in general population[24,25] but has not been used in studies of patients with LOBD. In addition, biomarkers, such as serum levels of homocysteine, vitamin B12, folate, and triiodothyronine, which are potential risk factors for both cerebrovascular diseases and cognitive dysfunction[26-28] have rarely been examined in LOBD.

Considering the inconsistent results in the literature, the aim of the study was to re-examine the difference of cognitive function between older people with LOBD and EOBD by rigorous vascular risk burden evaluation, carrying out comprehensive

cognitive tests, using newer definition of LOBD proposed by International Society for Bipolar Disorders Task force[3] and relevant biochemistry data. In order to assess the vascular risk burden more comprehensively compared to the prior studies,[13,15,18] we applied a series of vascular risk assessments including the individual cardiovascular disease, 10-year Framingham cardiovascular risk scores, and serum biomarkers such as homocysteine, vitamin B12, folate, and triiodothyronine.

2. Methods

2.1 Participants

We recruited older people with BD from the outpatient psychiatric services of four hospitals in Taipei City, and participants received a structured interview for diagnosis, relevant demographic and clinical data, laboratory examination, and a series of cognitive tests.

Inclusion criteria for the participants were as follows: (1) age≧55 years; (2) a primary diagnosis of bipolar I disorder (BD-I) confirmed by two research psychiatrists (S.C.L and C.C.C) according to the Structured Clinical Interview for DSM IV-TR Axis-I Disorder (SCID); and (3) capacity to provide informed consent. Exclusion criteria were: (1) severe or acute medical illness within the 3 months preceding the study; (2) neurological disorders such as delirium, Parkinson's disease, aphasia or multiple sclerosis; (3) dementia or a Mini-Mental State Examination (MMSE) score <17;[29] (4) alcoholism defined by an Alcohol Use Disorders Identification Test score ≧8 in males or ≧6 in females;[30] or (5) electroconvulsive therapy in the preceding year. All participants provided written informed consent, and the study was approved by the institutional review boards of Taipei City Hospital, Taipei Medical University-Wan Fang Hospital, Cathay General Hospital, and Mackay Memorial Hospital.

2.2 Exposure and covariate ascertainment

For all participants, a structured questionnaire was used to collect demographic and health-related factors, including age, sex, duration (years) of education, current cigarette smoking status, psychiatric history, physical health problems, and current pharmacotherapy. In addition, the Young Mania Rating Scale (YMRS)[31] and 17-item Hamilton Depression Rating Scale (HDRS)[32] were applied to measure the severity of manic and depressive symptoms, respectively. In this study, the onset of BD-I was defined as the first occurrence of affective symptoms, either depression or mania, which caused severe impairment of a participant's psychosocial function or resulted in psychiatric hospitalization. With the considerations that patients with BD actually have earlier onset of medical diseases and shorter life span, we used the 40 years-old as the cut-off age for EOBD and LOBD as recently proposed by International Society for Bipolar Disorders Task force.[3]

To evaluate general health status, self-reported history of the following symptoms/disorders was ascertained: angina, previous stroke, arthritis, asthma, bowel problems, cough, diabetes, poor eyesight, headaches, poor hearing, previous heart attack, hypertension, skin problems, and insomnia;[33,34] the total number of these symptoms/disorders was calculated. In addition, each participant also underwent measurement of blood pressure, body weight, and body height. Blood samples were

collected between 6:00 a.m. and 12:00 a.m. following overnight fasting. Serum homocysteine was measured by Novel enzyme cycling assay, and triiodothyronine was carried out by Chemiluminescence. Electrochemiluminescence assays were applied to analyze the levels of vitamin B12 and folate. As an overall measure of vascular risk status, 10-year Framingham risk scores were calculated from age, gender, current status of cigarette smoking, diabetes mellitus, treatment of hypertension, systolic blood pressure, and blood levels of high-density lipoprotein-cholesterol.[35]

2.3 Assessment of cognitive function

After enrollment, participants were administered the Mini-Mental State Examination (MMSE) as well as a series of the following cognitive tests: (1) word list subtest of Wechsler Memory Scale-III (WMS-III; verbal memory); (2) color trail test-1 (CTT-1; attention and psychomotor speed); (3) CTT-2 (cognitive flexibility and executive function); (4) block design score from the WAIS-III (visuospatial processing); (5) verbal fluency (semantic verbal fluency); (6) digit symbol substitution test (attention and psychomotor speed). In addition to global cognitive function from the MMSE, the following eight cognitive parameters were selected for final comparisons based on their theoretical representativeness of cognitive domains, observed sensitivity to age and education, and factor analysis[36] : total immediate recall, delayed recall, and recognition from word list subtest of WMS-III; CTT-1

completion time and CTT-2 completion time from CTTs; block design score from the WAIS-III; verbal fluency score from the fruit naming test; and digit symbol substitution test score from WAIS-III.

2.4 Statistical analyses

Comparisons between EOBD and LOBD groups were analyzed using independent sample *t* tests or Mann-Whitney U tests when explanatory variables were continuous. Pearson's $\chi 2$ tests or Fisher's exact tests were applied to comparisons of categorical variables. Multiple linear regressions were separately performed to examine the effect of EOBD and LOBD on individual cognitive parameter scores (dependent variables). Bearing in mind the limited sample size and number of potential covariates, only those with a clear potential impact on the associations between exposure and outcome (defined as p-value $\leqq 0.2$ when individual variable was put into simple linear regression to test its effect on the association between EOBD/LOBD and individual cognitive test) were in the final model. Through this, the variables adjusted in the regression model were age, gender, years of education, duration of illness, 10-year Framingham cardiovascular risk scores, and serum levels of homocysteine and triiodothyronine. Data analyses were performed using SPSS version 17.0 software, and statistical significance was defined as p-values smaller than 0.05 (two-sided).

3. Results

3.1 Inclusion of patients

Ninety-seven older adults with BD were enrolled in this study. Two of the participants did not complete the whole assessment and data from 95 participants were thus analyzed: 45 with EOBD and 50 with LOBD.

3.2 Demographic and clinical characteristics

Table 1 summarizes comparisons of demographic and clinical variables between the two groups. No significant differences were found with respect to age, gender, duration of education, severity of manic or depressive symptoms, family history of psychosis or dementia, or different categories of psychotropic treatments. Compared to EOBD, participants with LOBD had lower diastolic pressure and lower levels of homocysteine, but had higher levels of cholesterol. In addition, those with LOBD had lower body mass index and higher triiodothyronine levels at borderline significance levels. There was no difference of Framingham risk scores between EOBD and LOBD groups (mean±SD; 17.5±11.2 vs. 20.3±13.5, p=0.338). The correlations between serum homocysteine levels and other variables were examined. Homocysteine levels were not significantly correlated with age (γ=0.19, p=0.279) or educational years (γ=0.05, p=0.775), nor with other demographic and clinical variables.

[Insert Table 1 about here]

3.3 Cognitive performance

Table 2 summarizes comparisons of cognitive test scores between the two groups. Participants with LOBD had similar performance in every cognitive test to those with EOBD.

[Insert Table 2 about here]

3.4 Impact of explanatory variables on individual cognitive tests

When multiple linear regression analyses were separately performed for individual cognitive parameters to examine the impact of potential factors on associations of interest (Table 3), LOBD was not significantly associated with performance on any cognitive parameter. In contrast, age was positively associated with the scores of CCT-2, and negatively associated with the scores of block design and DSST. Years of education were positively associated with the scores of total immediate recall, delayed recall, recognition, block design, verbal fluency, DSST, and MMSE, and were negatively associated with the scores of CCT-1 and CCT-2. Further,

serum levels of homocysteine were positively associated with the scores of CCT-1, and were negatively associated with the scores of delayed recall, verbal fluency, and DSST. Duration of illness was negatively associated with the scores of delayed recall.

[Insert Table 3 about here]

In addition, we conducted an analysis using 50 years-old as the cut-off point for LOBD. The results are nearly the same with cut-off point set as 40 year-old for LOBD. It showed that serum levels of homocysteine were positively associated with the scores of CCT-1 (ß=0.29, p=0.012), and were negatively associated with the scores of delayed recall (ß=-0.27, p=0.023), verbal fluency (ß=-0.24, p=0.047), and DSST (ß=-0.25, p=0.013) in multiple linear regression model. Age was positively associated with the scores of CCT-2 and negatively associated with the scores of block design and DSST. Years of education were positively associated with the scores of total immediate recall, delayed recall, recognition, block design, verbal fluency, DSST, and MMSE, and were negatively associated with the scores of CCT-1 and CCT-2. No associations were found between cognitive test parameters and gender, LOBD, Framingham risk score, and serum triiodothyronine levels.

4. Discussion

One of the principal findings in the present study was that the performance of cognitive function in older patients with LOBD (i.e. defined by an onset above age 40 years) was not different from those with EOBD. The lack of association between age of onset and cognitive dysfunction is in line with some of prior reports[17,18] but not with others suggesting greater cognitive impairment in people with later age of BD onset.[15,16] Although we adopted 40 year-old as a decreased cut-off age for LOBD as proposed by the International Society for Bipolar Disorder Task force, the results of study interest are nearly the same as cut-off age of 50 year-old for LOBD in this sample. Previously, cardiovascular risk/diseases have been suggested to play an important role in the cognitive impairment in LOBD.[3] Our recent neuroimaging study found that one third of older BD patients with onset prior to the age of 40 years (i.e. EOBD) had cerebral infarction or old stroke.[37] The findings suggest that even older patients with EOBD are at a high risk of cerebrovascular diseases. In this study, compared to patients with LOBD, those with EOBD had similar Framingham risk scores and higher diastolic pressure but lower cholesterol levels. The similar cardiovascular risks/diseases between LOBD and EOBD groups in our sample might play a role for the lack of difference in cognitive function between the two groups.

In this study, in addition to age and education, the most consistent and significant finding was that higher serum homocysteine levels were significantly associated with worse performance in cognitive measures, including attention and psychomotor speed (CTT-1 and DSST), verbal memory(delayed recall), and executive function(verbal fluency and DSST). Among a variety of cognitive domains, executive dysfunction and verbal memory impairment are the cognitive deficits most consistently observed in patients with BD.[4-6,8] Prior studies of younger population with BD have also demonstrated that increased homocysteine levels were associated with cognitive deficits, particularly verbal learning, delayed memory, and executive function.[38-40] In addition, the adverse impact of homocysteine on cognition tended to be greater with the aging in patients with BD.[38] Taken together, our study was consistent with the previous researches suggesting that the elevated homocysteine levels could exert detrimental effects on the neurocognitive outcomes in patients with BD across the adult lifespan. Higher homocysteine levels in EOBD group may be another explanation for no difference of cognitive function between LOBD and EOBD groups in our study. In the present study, no significant association was found between global cognitive function, represented by MMSE score, and homocysteine levels. Whether homocysteine is consistently associated with some specific cognitive domains, such

as attention, psychomotor speed, verbal memory and executive function, as suggested in this study, needs further investigation.

The mechanisms underlying the association between elevated serum levels of homocysteine and cognitive dysfunctions in older patients with BD are unclear. In previous studies, serum homocysteine was found to be elevated in acute manic episodes of BD.[41] A recent meta-analysis has concluded that serum homocysteine levels are elevated in patients with BD even during the euthymic state.[42] These findings suggest that homocysteine is both a trait and state biomarker for patients with BD. In the studies of elderly general population, the serum levels of homocysteine over 11umol/L were found to be associated with the increased risk of dementia and atrophy of medial temporal lobe.[43,44] The elevated levels of homocysteine potentially lead to cognitive dysfunctions due to the activations of inflammatory and oxidative stress pathways or the reactivations of cholinergic metabolism[45,46] as well as being a potential vascular risk factor itself.[47] In our study, the mean serum levels of homocysteine in either LOBD or EOBD group were actually above 11umol/L, and therefore may account for the link to cognitive dysfunctions.

In line with previous studies,[2,6,8] our data confirmed that increased age was associated with cognitive dysfunctions in patients with BD. In particular, the negative association between age and DSST performance in our multivariate analyses was

similar to that reported by Lewandowski et al.,[6] indicating particular impairments of information processing speed in aged people with BD. Longer duration of education was associated with better performance on all cognitive function domains in our participants. Recently, large-sample studies in BD have reported that higher cognitive reserve is associated with better psychosocial functioning and cognitive performance with respect to processing speed, working memory, verbal and visual memory, and executive function.[10,11] In the present sample, the mean years of education were 11.3±4.1 and 9.9±4.1 for EOBD and LOBD, respectively. The lengths of education in our participants were similar to those of other Taiwanese samples,[2,5] although relatively shorter than those reported in Western BD populations.[4,6,13,15] Considering lower educational levels in Eastern older populations with BD, utilization of other proxy variables, such as the Intelligent Quotient and occupational attainment, rather than educational years may be more helpful to investigate cognitive reserve in future studies.

Compared to prior investigations, strengths of the present study included comprehensive assessments of vascular risk burden, a broad range of neuropsychological tests covering cognitive domains, and ascertainment of BD using a structured diagnostic interview. However, there were several methodological limitations that need to be considered when interpreting our findings. First, this study

was cross-sectional in design and direction of causation cannot be inferred. Second, there was no control group without BD included in this study, which make the results difficult to compare with general population. Third, the participants were recruited from psychiatric outpatient services and the distribution of MMSE total scores was higher than those reported in other studies of Taiwanese older patients with BD.[2,5] Our sample may therefore represent a subgroup of older patients with BD who function relatively well in the community. Fourth, multiple comparisons were carried out to test the association of LOBD or other important variables with cognitive performance, which may lead to type I error.

5. Conclusion

In summary, our data suggest that the later age of onset may not be associated with more severe cognitive dysfunction in older population with BD. In addition, we found that the higher serum homocysteine levels were significantly associated with worse cognitive performance in older patients with BD. Considering that patients with BD may have poor self-care ability and worse life quality at older age because of cognitive impairments, clinicians have to pay more attention to the cognitive function in older BD patients with higher levels of homocysteine. Further researches are warranted to investigate the role of homocysteine in the pathogenesis of neurocognitive deficits in patients with BD.

Acknowledgements

This work is supported by Taipei City Hospital and the Ministry of Science and Technology (MOST 105-2314-B-532-003-MY3) of Taiwan; and RS is part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre, Dementia Biomedical Research Unit at South London and Maudsley NHS Foundation Trust, and King's College London of UK.

We thank Ms. Su-Chen Chang and Ms. Chia-Chen Hsu for their excellent work on participant recruitment, laboratory work, and data management. We especially thank all participants who agreed to join this study.

Conflict of interest

All authors declare no conflict of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Gildengers AG, Whyte EM, Drayer RA, et al. Medical burden in late-life bipolar and major depressive disorders. *Am J Geriatr Psychiatry*. 2008;16(3):194–200.
2. Tsai SY, Kuo CJ, Chung KH, Huang YL, Lee HC, Chen CC. Cognitive dysfunction and medical morbidity in elderly outpatients with bipolar disorder. *Am J Geriatr Psychiatry*. 2009;17(12):1004–1011.
3. Sajatovic M, Strejilevich SA, Gildengers AG, et al. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disord*. 2015;17(7):689–704.
4. Gildengers AG, Butters MA, Seligman K, et al. Cognitive functioning in late-life bipolar disorder. *Am J Psychiatry*. 2004;161(4):736–738.
5. Tsai SY, Lee HC, Chen CC, Huang YL. Cognitive impairment in later life in patients with early-onset bipolar disorder. *Bipolar Disord*. 2007;9(8):868–875.
6. Lewandowski KE, Sperry SH, Malloy MC, Forester BP. Age as a predictor of cognitive decline in bipolar disorder. *Am J Geriatr Psychiatry*. 2014;22(12):1462–1468.
7. Diniz BS, Teixeira AL, Cao F, et al. History of bipolar disorder and the risk of dementia: A systematic review and meta-Analysis. *Am J Geriatr Psychiatry*. 2017;25(4):357–362.

8. Samamé C, Martino DJ, Strejilevich SA. A quantitative review of neurocognition in euthymic late-life bipolar disorder. *Bipolar Disord*. 2013;15(6):633–644.
9. Ospina LH, Russo M, Nitzburg GM, et al. The effects of cigarette smoking behavior and psychosis history on general and social cognition in bipolar disorder. *Bipolar Disord*. 2016;18(6):528–538.
10. Anaya C, Torrent C, Caballero FF, et al. Cognitive reserve in bipolar disorder: relation to cognition, psychosocial functioning and quality of life. *Acta Psychiatr Scand*. 2016;133(5):386–398.
11. Hinrichs KH, Easter RE, Angers K, et al. Influence of cognitive reserve on neuropsychological functioning in bipolar disorder: Findings from a 5-year longitudinal study. *Bipolar Disord*. 2017;19(1):50–59.
12. Gildengers AG, Mulsant BH, Al Jurdi RK, et al. The relationship of bipolar disorder lifetime duration and vascular burden to cognition in older adults. *Bipolar Disord*. 2010;12(8):851–858.
13. Schouws SN, Stek ML, Comijs HC, Beekman AT. Risk factors for cognitive impairment in elderly bipolar patients. *J Affect Disord*. 2010;125(1–3):330–335.
14. Huang SH, Chung KH, Hsu JL, Wu JY, Huang YL, Tsai SY. The risk factors for elderly patients with bipolar disorder having cerebral infarction. *J Geriatr Psychiatry Neurol*. 2012;25(1):15–19.

15. Schouws SN, Comijs HC, Stek ML, et al. Cognitive impairment in early and late bipolar disorder. *Am J Geriatr Psychiatry*. 2009;17(6):508–515.

16. Martino DJ, Strejilevich SA, Manes F. Neurocognitive functioning in early-onset and late-onset older patients with euthymic bipolar disorder. *Int J Geriatr Psychiatry*. 2013;28(2):142–148.

17. Depp CA, Jin H, Mohamed S, Kaskow J, Moore DJ, Jeste DV. Bipolar disorder in middle-aged and elderly adults: is age of onset important? *J Nerv Ment Dis*. 2004;192(111):796–799.

18. Subramaniam H, Dennis MS, Byrne EJ. The role of vascular risk factors in late onset bipolar disorder. *Int J Geriatr Psychiatry*. 2007;22(8):733–737.

19. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? *J Neurol Neurosurg Psychiatry*. 2004;75(12):1662–1666.

20. Gildengers AG, Chung KH, Huang SH, Begley A, Aizenstein HJ, Tsai SY. Neuroprogressive effects of lifetime illness duration in older adults with bipolar disorder. *Bipolar Disord*. 2014;16(6):617–623.

21. Rusanen M, Kivipelto M, Levälahti E, et al. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. *J Alzheimers Dis*. 2014;42(1):183–191.

22. Gardener H, Wright CB, Rundek T, Sacco RL. Brain health and shared risk factors for dementia and stroke. *Nat Rev Neurol*. 2015;11(11):651–657.

23. Cassidy F, Carroll BJ. Vascular risk factors in late onset mania. *Psychol Med*. 2002;32(2):359–362.

24. Kaffashian S, Dugravot A, Elbaz A, et al. Predicting cognitive decline: a dementia risk score vs. the Framingham vascular risk scores. *Neurology*. 2013;80(14):1300–1306.

25. Viticchi G, Falsetti L, Buratti L, et al. Framingham risk score and the risk of progression from mild cognitive impairment to dementia. *J Alzheimers Dis*. 2017;59(1):67–75.

26. Tay SY, Ampil ER, Chen CP, Auchus AP. The relationship between homocysteine, cognition and stroke subtypes in acute stroke. *J Neurol Sci*. 2006;250(1–2):58–61.

27. Jiang B, Chen Y, Yao G, et al. Effects of differences in serum total homocysteine, folate, and vitamin B12 on cognitive impairment in stroke patients. *BMC Neurol*. 2014;14:217.

28. Bunevicius A, Kazlauskas H, Raskauskiene N, Janusonis V, Bunevicius R. Ischemic stroke functional outcomes are independently associated with C-reactive protein concentrations and cognitive outcomes with triiodothyronine

concentrations: a pilot study. *Endocrine*. 2014;45(2):213–220.

29. Alexopoulos GS, Meyers BS, Young RC, et al. Executive dysfunction and long-term outcomes of geriatric depression. *Arch Gen Psychiatry*. 2000;57(3):285–290.

30. Chen CH, Chen WJ, Cheng AT. New approach to the validity of the alcohol use disorders identification test: stratum-specific likelihood ratios analysis. *Alcohol Clin Exp Res*. 2005;29(4):602–608.

31. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429–435.

32. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;2:56–62.

33. Prince MJ, Harwood RH, Blizard RA, Thomas A, Mann AH. Social support deficits, loneliness and life events as risk factors for depression in old age. The Gospel Oak Project VI. *Psychol Med*. 1997;27(2):323–332.

34. Stewart R, Russ C, Richards M, Brayne C, Lovestone S, Mann A. Depression, APOE genotype and subjective memory impairment: a cross-sectional study in an African-Caribbean population. *Psychol Med*. 2001;31(3):431–440.

35. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*.

2008;117(6):743–753.

36. Chu CS, Sun IW, Begum A, et al. The association between subjective memory complaint and objective cognitive function in older people with previous major depression. *PLoS One*. 2017;12(3):e0173027.

37. Lee HC, Hsu JL, Chen PH, Chung KH, Huang YJ, Tsai SY. High risk of silent stroke in older bipolar patients with typical-onset age. *Psychogeriatrics*. 2019; doi: 10.1111/psyg.12419.

38. Dias VV, Brissos S, Cardoso C, Andreazza AC, Kapczinski F. Serum homocysteine levels and cognitive functioning in euthymic bipolar patients. *J Affect Disord*. 2009;113(3):285–290.

39. Dittmann S, Seemüller F, Grunze HC, et al. The impact of homocysteine levels on cognition in euthymic bipolar patients: a cross-sectional study. *J Clin Psychiatry*. 2008;69(6):899–906.

40. Osher Y, Bersudsky Y, Silver H, Sela BA, Belmaker RH. Neuropsychological correlates of homocysteine levels in euthymic bipolar patients. *J Affect Disord*. 2008;105(1–3):229–233.

41. Ozbek Z, Kucukali CI, Ozkok E, et al. Effect of the methylenetetrahydrofolate reductase gene polymorphisms on homocysteine, folate and vitamin B12 in patients with bipolar disorder and relatives. *Prog Neuropsychopharmacol Biol*

Psychiatry. 2008;32(5):1331–1337.

42. Salagre E, Vizuete AF, Leite M, et al. Homocysteine as a peripheral biomarker in bipolar disorder: A meta-analysis. *Eur Psychiatry*. 2017;43:81–91.
43. Ravaglia G, Forti P, Maioli F, et al. Homocysteine and folate as risk factors for dementia and Alzheimer disease. *Am J Clin Nutr*. 2005;82(3):636–643.
44. Oulhaj A, Refsum H, Beaumont H, et al. Homocysteine as a predictor of cognitive decline in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2010;25(1):82–90.
45. Pirchl M, Ullrich C, Humpel C. Differential effects of short- and long-term hyperhomocysteinaemia on cholinergic neurons, spatial memory and microbleedings in vivo in rats. *Eur J Neurosci*. 2010;32(9):1516–1527.
46. Koz ST, Etem EO, Baydas G, et al. Effects of resveratrol on blood homocysteine level, on homocysteine induced oxidative stress, apoptosis and cognitive dysfunctions in rats. *Brain Res*. 2012;1484:29–38.
47. Huang X, Li Y, Li P, et al. Association between percent decline in serum total homocysteine and risk of first stroke. *Neurology*. 2017;89(20):2101–2107.

Tables

Table 1. Comparison of sociodemographic and clinical characteristics between EOBD and LOBD

	EOBD (N=45)		LOBD (N=50)			
Continuous variables	**Mean**	**SD**	**Mean**	**SD**	**t**	**P**
Age, years	62.3	3.7	63.8	5.9	-1.53	0.129
Education, years	11.3	4.1	9.9	4.1	1.64	0.105
Bipolar characteristics						
Age of first mania, years	30.0	14.1	53.3	7.1	-8.92	0.001
Age of first depression, years	27.5	12.0	52.2	7.3	-9.14	0.001
Duration of illness, years	38.4	9.1	11.3	8.1	15.35	0.001
YMRS total score	3.4	2.7	3.7	3.2	-0.73	0.470
HAMD total score	5.3	5.2	5.3	4.4	0.051	0.959
Physical health status						
Total number of symptoms	4.47	2.43	4.58	2.36	-0.23	0.818
Body mass index, kg/m^2	26.7	3.7	25.3	3.9	1.78	0.079
Systolic blood pressure, mmHg	125.6	21.6	122.8	16.7	0.64	0.523
Diastolic blood pressure, mmHg	78.1	12.4	72.5	10.7	2.19	0.031

Fasting glucose levels, mg/dL	104.5	22.8	111.1	41.8	-0.94	0.349
Triglycerides levels, mg/dL	142.0	79.3	166.5	116.5	-1.18	0.242
Total cholesterol levels, mg/dL	185.7	39.0	203.5	43.4	-2.10	0.039
HDL-C levels, mg/dL	50.5	14.3	51.5	21.4	-0.28	0.781
Homocysteine levels, umol/L	15.0	6.2	12.2	4.2	2.56	0.012
Vitamin B12 levels, pg/mL	583.8	328.6	654.5	304.8	-1.10	0.287
Folate levels, ng/mL	12.0	4.5	10.6	4.3	1.42	0.158
Triiodothyronine levels, ng/ml	0.97	0.19	1.04	0.17	-1.85	0.068
Category variables	**N**	**%**	**N**	**%**	**χ^2**	**p**
Male	22	48.9	29	58.0	0.79	0.374
Married/widowed	33	73.3	32	69.6	2.51	0.102
Current smoker	9	20.5	12	24.0	0.97	0.617
Family history						
Psychosis	5	11.9	11	22.4	1.74	0.188
Dementia	5	11.6	7	14.2	0.14	0.706
Psychotropic medications						
Mood stabilizer	31	79.5	28	68.3	1.29	0.255
First generation antipsychotics	2	5.1	6	14.6	2.01	0.157
Second generation antipsychotics	16	41.0	19	46.3	0.23	0.632

Antidepressant	18	46.1	25	60.9	1.77	0.184
Physical health status						
Angina	1	2.2	3	6.0	0.84	0.360
Hypertension	20	44.4	20	40.0	1.04	0.596
Diabetes mellitus	16	35.6	11	22.0	2.14	0.144

Abbreviations: EOBD=early-onset bipolar disorder, HAMD=Hamilton Depression Rating Scale, HDL-C=high-density lipoprotein-cholesterol, LOBD=late-onset bipolar disorder, YMRS= Young Mania Rating Scale

Table 2. Comparison of cognitive functions between EOBD and LOBD

	EOBD (N=45)		LOBD (N=50)			
Cognitive tests	**Mean**	**SD**	**Mean**	**SD**	**t**	**P**
Total immediate recall	24.0	7.8	24.0	5.7	-0.03	0.977
Delayed recall	4.5	3.0	4.5	2.4	-0.14	0.989
Recognition	21.1	3.1	21.2	2.4	-0.20	0.842
CTT-1, seconds	83.6	57.0	76.8	41.2	0.67	0.502
CTT-2, seconds	143.1	65.7	146.2	63.2	-0.24	0.812
Block design	24.8	11.6	24.4	10.2	0.17	0.865
Verbal Fluency	12.0	4.5	12.5	4.1	-0.59	0.554
DSST	44.1	19.1	42.7	17.4	0.39	0.700
MMSE	26.3	3.2	25.9	2.7	0.60	0.549

Abbreviations: CTT=Color Trail Test, DSST= Digit Symbol Substitution Test, EOBD=early-onset bipolar disorder, LOBD=late-onset bipolar disorder, MMSE= Mini-Mental State Examination

Table 3. Multiple linear regressions for the impact of explanatory variables on cognitive test parameters

	Total immediate recall			**Delayed recall**			**Recognition**		
Explanatory variables	**B-coefficient**	**β**	***p* value**	**B-coefficient**	**β**	***p* value**	**B-coefficient**	**β**	***p* value**
Age	0.10±0.16	0.08	0.531	0.13±0.07	0.23	0.062	0.02±0.07	0.05	0.737
Gender	-3.61±1.94	-0.26	0.067	-0.94±0.78	-0.17	0.233	-0.70±0.83	-0.13	0.404
Years of education	0.79±0.19	0.47	0.001	0.27±0.08	0.39	0.001	0.19±0.08	0.29	0.023
LOBD	-4.40±3.00	-0.32	0.148	-2.19±1.21	-0.39	0.075	-1.21±1.29	-0.23	0.351
Duration of illness	-0.18±0.09	-0.41	0.061	-0.08±0.04	-0.45	0.037	-0.05±0.04	-0.29	0.221
Framingham risk score	-0.03±0.08	-0.06	0.686	-0.03±0.03	-0.14	0.343	-0.02±0.04	-0.07	0.656
Homocysteine levels	-0.18±0.15	-0.14	0.220	-0.15±0.06	-0.28	0.018	-0.05±0.06	-0.11	0.419
Triiodothyronine levels	0.26±0.52	0.06	0.619	0.08±0.21	0.04	0.718	-0.03±0.22	-0.02	0.886

	CTT-1			CTT-2			Block design		
Explanatory variables	**B-coefficient**	**β**	***p* value**	**B-coefficient**	**β**	***p* value**	**B-coefficient**	**β**	***p* value**
Age	0.85±1.09	0.09	0.437	3.51±1.36	0.29	0.012	-0.63±0.27	-0.28	0.023
Gender	5.26±12.89	0.05	0.685	15.63±15.98	0.13	0.332	3.11±3.19	0.14	0.333
Years of education	-6.06±1.27	-0.51	0.001	-8.05±1.59	-0.52	0.001	1.12±0.31	0.40	0.001
LOBD	19.86±19.99	0.20	0.324	19.61±24.82	0.16	0.432	-1.41±4.94	-0.06	0.776
Duration of illness	0.86±0.62	0.28	0.171	0.68±0.77	0.17	0.381	-0.10±0.15	-0.14	0.508
Framingham risk score	-0.76±0.54	-0.19	0.168	-0.54±0.67	-0.11	0.428	-0.05±0.13	-0.05	0.716
Homocysteine levels	2.54±0.99	0.28	0.013	1.98±1.23	0.17	0.114	-0.21±0.25	-0.10	0.386
Triiodothyronine levels	2.96±3.46	0.09	0.396	0.60±4.31	0.01	0.890	0.01±0.86	0.01	0.990

	Verbal Fluency			DSST			MMSE		
Explanatory variables	**B-coefficient**	**β**	***p* value**	**B-coefficient**	**β**	***p* value**	**B-coefficient**	**β**	***p* value**
Age	-0.11±0.11	-0.13	0.296	-1.14±0.38	-0.31	0.004	-0.11±0.07	-0.19	0.120
Gender	-0.38±1.26	-0.04	0.761	-0.08±4.47	-0.01	0.986	0.54±0.83	0.09	0.520
Years of education	0.36±0.12	0.33	0.005	2.65±0.44	0.58	0.001	0.34±0.08	0.47	0.001
LOBD	-1.84±1.94	-0.21	0.346	2.18±6.93	0.06	0.754	-0.22±1.28	-0.04	0.862
Duration of illness	-0.09±0.06	-0.31	0.154	-0.02±0.26	-0.02	0.929	-0.01±0.04	-0.07	0.760
Framingham risk score	-0.01±0.05	-0.04	0.793	-0.05±0.19	-0.03	0.809	0.02±0.04	0.06	0.678
Homocysteine levels	-0.20±0.10	-0.25	0.041	-0.78±0.34	-0.23	0.026	-0.06±0.06	-0.11	0.333
Triiodothyronine levels	0.41±0.34	0.14	0.230	0.58±1.20	0.05	0.631	-0.10±0.22	-0.05	0.661

Abbreviations: CTT=Color Trail Test, DSST= Digit Symbol Substitution Test, LOBD=late-onset bipolar disorder, MMSE= Mini-Mental State Examination